

## Introduction

Despite some risks of a seasonal nature, we opted to locate the ISN Forefronts Symposium on Molecular and Cellular Mechanisms of Renin-Angiotensin Synthesis and Release in the 'Far North of Australia' (Port Douglas, Queensland), which was held on March 27-30, 1993. We were surrounded by tropical rainforest containing exotic native birds, fauna and flora which embrace one of the wonders of the world: The Great Barrier Reef. The advantage of this idyllic location was that registrants were isolated, but there was a slight disadvantage in that travel arrangements were complex. Because the Forefronts meeting was fortuitously held immediately after the 15th International Society of Hypertension meeting, our registrants and key speakers were able to save significantly on travel expenditures to attend.

To understand the *raison d'être* for this Forefronts meeting, one must ask if we really know how the incredibly therapeutic ACE inhibitors work effectively. The answer is no: We must ponder how they work. By our criteria, we believe this meeting was a great success. The work presented was current, the discussions were critical and robust, but all was in the spirit of scientific inquiry and good will.

In this Symposium issue Michael McKinley focuses our attention on the roles of angiotensin II in the central nervous system, from its classical role in drinking and thirst to its importance in blood pressure regulation and regulation of renin secretion and release. The primacy of central regulation over local changes needs much further investigation. Professor Mendelsohn's paper elegantly demonstrates that endogenously produced angiotensin II can interfere *in vivo* with access to receptors by agonists and inhibitors, a very important consideration when interpreting *in vivo* experiments.

Dr. de Gasparo's scholarly review of the angiotensin receptor field sets the stage for several papers which polish our knowledge of angiotensin II receptors. AT<sub>2</sub> receptors overlap in terms of distribution; they are not internalized and seem to be quite separate in terms of their lack of recognized function, which remains an enigma. AT<sub>2</sub> receptor(s) may act by inhibiting phosphotyrosine phosphatase.

Despite our detailed knowledge of angiotensin II receptors, the difference between AT<sub>1</sub> receptors which differentiate between the potency of angiotensin II and III on the one hand (for example, smooth muscle), and those which do not (for example, adrenal) has not been resolved by the AT<sub>1A</sub>/AT<sub>1B</sub> classification. Harding's persuasive studies on the AT<sub>4</sub> receptor await further elucidation of another agonist(s). The key question is whether or not the hexapeptide A1-6 is the true agonist. Is it locally produced by C terminal peptidases? Is C terminal metabolism a major route in the fate of angiotensin II?

Analyses of the upstream regulation of the renin gene are providing valuable insight into the control of this gene expression. However, it is too soon to determine the role of renin expression in the cellular mechanisms which cause production of angiotensin II, particularly in the central nervous system, and the role of renal

renin gene expression in the replacement of secretory granules in the kidney and the mechanisms of the response to sodium depletion or angiotensin II inhibition. In fact, processing secretion and storage are arenas where much needs to be done, which is illuminated in the paper by Reudelhuber. Dr. Takahashi reviews ten years of work on the specific high-affinity renin binding protein. The renin binding protein joins others with a leucine zipper motif.

Despite great advances in these areas, a constellation of questions spring to mind. What regulates processing enzymes? Is the renin secretory process the same as most other secreted proteins? What is the role of such a high-affinity specific binding protein? Is renin taken back up at renal and other sites? The renin binding protein is not confined to the kidney.

A particular focus of studies about the renin-angiotensin system in the molecular idiom is the place of transgenic animals, where either programmed oversecretion is a goal, or gene knockout where a gene in a homologous strain is deleted. The literature abounds with examples where application of this complex technology has been extremely valuable. Far too many examples also exist where only a very sophisticated model of infusion at a high level is achieved, or where complex mechanisms to activate the transgene have operated poorly. Obviously, cross species transgenes may provide a useful hypertensive model. The fascinating work of Caroline Whitworth might be further enhanced by concurrent studies of sodium status.

In the crossover renal transplantation experiment of Dr. Rettig or in the renal clip experiments of Dr. Kurtz, despite the complexity of the designs, local production of renin and its influence on angiotensin II concentration and receptor numbers are highlighted, as well as the importance of the preprogrammed phenotype.

The literature relating to these issues originates with the earliest studies of Goldblatt in 1934. The subject is complex, ambiguous and fraught with design and interpretive differences. Nonetheless, as "old men of the tribe" we feel that close scrutiny of the early studies are worthwhile and can be very rewarding.

The series of papers on the angiotensinogen gene remind us of the multi-factorial nature of this interesting system, and again emphasizes that, while much is known a great deal awaits discovery. For example, the circulating level of angiotensinogen is highly regulated, but knowledge of how this is influenced, especially by sodium status, is scarce.

Dr. Phillips opens the door to antisense oligonucleotides as a new type of pharmacological inhibitor. Despite hypothetical concerns, these oligonucleotides seem to be extremely useful tools. There are now many cases of the successful use of antisense oligos in the literature.

The large number of meetings focusing on human hypertension and its treatment attest to the seriousness of the disease, the therapeutic complexity, and the enormous investment of the pharmaceutical industry. Because genes associated with the renin-angiotensin system have been recently shown to be associated with

hypertension and coronary heart disease, public health issues should loom larger in future research.

A variant of the angiotensin converting enzyme gene was found to be more frequent in cases of myocardial infarction, and the angiotensinogen gene appears to be linked to hypertension. Dr. Williams describes his studies as "complementary to physiologic analysis are genetic approaches, which are designed to identify mutations in genes which contribute to hypertension. A particularly useful approach is to determine intermediate phenotypes in essential hypertension and thus perform linkage analysis with candidate genes." Harrap reflects on two other approaches: the affected relative pairs method and four corners methodology. The Gordon group re-evaluates the incidence of primary aldosteronism in a highly selected cohort of patients and has a revealing analysis of tumor type. Each study illuminates an aspect of the renin-angiotensin system that is a departure from normal.

The organizers of this Forefronts Symposium acknowledge the fact that the meeting relied heavily on the trust of the ISN, and in

particular Professors Gerhard Giebisch and Klaus Thirau, to enable us to hold it in a site remote from Europe or the United States. We thank them for their confidence. Thanks also to Dr. Ian Darby, Dr. Ross Fernley, and Mrs. Lynn Turner for their efforts in organizing the conference. We greatly appreciate that Professor Giebisch attended the meeting, and we thank him for his generous remarks in his formal closure. In addition to the sponsorship of the International Society of Nephrology, this Forefronts in Nephrology meeting was supported by the AMRAD Corporation and the Howard Florey Institute of Experimental Physiology and Medicine. The Howard Florey Institute is supported by a block grant from the National Health and Medical Research Council of Australia and by generous support from private industry.

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